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COMPLETE SPECIFICATION.

Injectable Colloidal Iron Preparations and Their Production.

We, FARBENFABRIKEN BAYER AKTIENGESELLSCHAFT, a body corporate organised under the laws of Germany, of Leverkusen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with colloidal iron preparations and a novel method of production of said preparations. Iron preparations in which the iron has a valence of 3 are known to be useful in the treatment of various conditions in which administration of iron is required or indicated and also in the treatment of conditions in which there is a deficiency of iron. Colloidal iron preparations are known and are utilized in such treatment. Specifically, iron hydroxide-sugar preparations and preparations comprising iron having a valence of 3 together with dextran are known and used in such treatment.

According to German Patent No. 938,502 iron dextran preparations are produced by first degrading a crude dextran such as by the action of mineral acids at an elevated temperature. A mixture of polymer homologues is thereby obtained and it is from this that the desired complex forming fraction is obtained by the addition of polar solvents. By heating and adding ferric salts and liquors conversion into the desired complex occurs.

A new process for the preparation of injectable colloidal iron preparations has now been discovered which is superior to those heretofore known. According to the process of the present invention a polysaccharide which may be in alkaline, neutral or weakly acid solution is heated with hydrogen peroxide and, at a pH above 8, with a non-toxic ferric compound. The latter is generally one which can form ferric hydroxide at such a pH. A polysaccharide-iron complex is formed and this is brought into aqueous solution with or without the addition of chelate forming hydroxy acids. An injectable colloidal iron preparation may be prepared from the complex; means for doing this are known *per se*, such as neutralization, dialysis, desalting, etc. This injectable iron preparation may be used in the same way as known colloidal iron preparations and is suitable for use in the treatment of conditions which indicate the administration of iron preparations and for use in the treatment of iron deficiencies.

A wide variety of polysaccharides are equally suitable as starting materials in the present process and the particularly preferred polysaccharides are starch, dextrans, levans as well as other water soluble polysaccharides of the inulin and mannan and, preferably, pullulan type. The ferric salts which are used in the present process include all non-toxic ferric salts. Besides the water soluble ferric salts such as the nitrate, chloride, acetate and double salts such as ferric ammonium chloride, ferric oxy salts, and ferric compounds which can be converted into ferric hydroxide in the presence of alkali are equally suitable for use in the present process.

In carrying out the process of the present invention, it is not necessary to prepare suitable fractions with specific molecular weights from the starting materials but rather polysaccharides of any molecular weight can be used with equal facility. This presents a substantial advantage over known processes where it is necessary before commencing to select and prepare suitable fractions with specific molecular weight.

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More particularly the process of the present invention comprises rendering alkaline an aqueous solution of a polysaccharide by adjusting to a pH value higher than 8 and adding thereto hydrogen peroxide and an aqueous solution of a ferric salt. Alternatively, the aqueous solution of the polysaccharide can be rendered neutral or weakly acid and heated to boiling with hydrogen peroxide until degradation of the polysaccharide has reached the desired degree. At that stage reaction with ferric salts is effected at a pH above 8. Ferric hydroxide flocculates out initially, but rapidly goes colloidally into solution. This is readily observed from the fact that the brownish color of the finely divided ferric hydroxide changes into the brown-red color of the resulting complex.

The solution which is thereby obtained can be worked up into an injectable preparation by known means such as neutralization, dialysis, or desalting or by a suitable combination of these steps as desired.

The complex can be obtained from the solution in solid form if desired and this can be accomplished by precipitating the complex out with solvents, freeze drying or spray drying and thereby obtaining a complex which in certain circumstances may be virtually insoluble in water. To form an injectable solution from this complex small amounts of a chelate forming hydroxy acid or salt thereof are added when redissolving the complex in water. The following chelate forming hydroxy acids are particularly useful, namely citric acid, tartaric acid, lactic acid, glycolic acid, and salicylic acid, but it is to be appreciated that other chelate forming hydroxy acids are equally suitable. When a chelate forming hydroxy acid or salt is added it is preferred to add it in an amount of 2 to 10 per cent based on the weight of the polysaccharide iron complex.

The following non-limitative examples more particularly describe the colloidal iron preparation and the production thereof:

EXAMPLE 1

16.2 g water soluble starch are dissolved at 70°C. in 400 ml water, with stirring. To the solution are added 50 ml 2N sodium hydroxide solution and 10 ml 30% hydrogen peroxide. 67 ml of a 30% iron chloride solution are then added dropwise and stirring continued for 1 hour at 75°C. The mixture is clarified by centrifuging and neutralized to pH 7.5 with hydrochloric acid, freed from portions of low molecular weight by dialysis, precipitated with methanol and dried. An iron-starch complex is obtained.
Yield: 15.5 g; iron content 24.4%.

38 g of this iron-starch complex are warmed with 2 g secondary sodium citrate and about 80 ml water until solution occurs. The solution is then adjusted to pH 6.3, made up to 100 ml with water and rendered isotonic. Sterilization takes place by heating to 105°C. for half an hour. An injectable iron complex compound with a content of 100 mg iron per ml is obtained.

EXAMPLE 2

16.2 g dextran of high molecular weight (molecular weight 50,000) are, as described in Example 1, dissolved with the addition of sodium hydroxide solution, and 10 ml 30% hydrogen peroxide and 90 ml 30% iron chloride solution are added. An iron-dextran complex is obtained.
Yield: 16.0 g; iron content 21.2%.

The iron-dextran complex is then worked up into an injectable iron complex by the procedure set forth in Example 1.

EXAMPLE 3

16.2 g natural levan are, as described in Example 1, dissolved with the addition of sodium hydroxide solution, and 10 ml 30% hydrogen peroxide and 95 ml 30% iron chloride solution are added. An iron-levan complex is obtained.
Yield: 13.0 g; iron content 22.52%.

The iron-levan complex is worked up into an injectable iron complex by the procedure set forth in Example 1.

EXAMPLE 4

16.2 g levan of low molecular weight are, as described in Example 1, dissolved with the addition of sodium hydroxide solution, and 10 ml 30% hydrogen peroxide and 100 ml iron chloride solution are added; the mixture is kept alkaline by further addition of 2N sodium hydroxide solution. An iron-levan complex is obtained.
Yield: 19.7 g; iron content 25.3%.

The iron-levan complex is worked up into an injectable iron complex by the procedure set forth in Example 1.

EXAMPLE 5

16.2 g levan of low molecular weight are, as described in Example 1, dissolved with the addition of sodium hydroxide solution; 5 cc 30% hydrogen peroxide are added and the mixture is converted into the complex with 100 ml iron chloride solution. An iron-levan complex is obtained.
Yield: 9.85 g; iron content 32.5%.

The iron-levan complex is worked up into an injectable iron complex by the procedure set forth in Example 1.

EXAMPLE 6

16.2 g water soluble starch are dissolved in 400 ml water, and 2.5 ml 30% hydrogen peroxide are added. The mixture is then heated to the boil for 7 hours; 40 ml tri-

ethylamine are added and 70 ml of a 30% iron chloride solution are added dropwise. The mixture is further stirred for one hour at about 80°C., clarified by centrifuging and precipitated with methanol. After reprecipitation once from methanol, an iron-starch complex is obtained.

Yield: 12.8 g; iron content 24.8%.

40 g of the iron-starch complex are dissolved at elevated temperature in a little water and, after adjustment of the pH value to 6.3, made up to 100 ml. The solution is then rendered isotonic with sodium chloride. Sterilization takes place by heating to 105°C. for half an hour. An injectable solution of the iron complex with a content of 100 mg/ml iron is obtained.

EXAMPLE 7

16.2 g water soluble starch are dissolved in 400 ml water, and 10 ml 30% hydrogen peroxide are added. The solution is heated to the boil for 2½ hours and the procedure of Example 1 is followed to produce an iron-starch complex.

Yield: 14.0 g; iron content 25.4%.

The iron-starch complex is then worked up into an injectable iron complex according to the procedure set forth in Example 1.

EXAMPLE 8

16.2 g natural levan are dissolved in 400 ml water, 15 ml acetate buffer of pH 5.5, and 5.0 cc 30% hydrogen peroxide are added. The mixture is heated to boiling for 3 hours and an iron-levan complex is obtained according to the procedure set forth in Example 1.

Yield: 13.2 g; iron content 25.8%.

The iron-levan complex is then worked up into an injectable iron complex according to the procedure set forth in Example 1.

WHAT WE CLAIM IS:—

1. A process for the production of a colloidal iron preparation which comprises heating a polysaccharide with hydrogen peroxide and, at a pH above 8, with a non-toxic ferric compound whereby there is formed a polysaccharide-iron complex, and bringing the complex into solution to form a colloidal iron preparation.

2. A process according to claim 1 wherein the polysaccharide is starch, dextran, levan, inulin, mannan or pullulan.

3. A process according to claim 1 or 2 wherein the ferric compound is ferric nitrate, ferric chloride, ferric acetate, ferric ammonium chloride or a ferric oxy salt.

4. A process according to any of claims 1—3 wherein the polysaccharide is in alkaline solution when heated with the hydrogen peroxide.

5. A process according to any of claims 1—3 wherein the polysaccharide is in neutral solution when heated with the hydrogen peroxide.

6. A process according to any of claims 1—3 wherein the polysaccharide is in a weak acid solution when heated with the hydrogen peroxide.

7. A process according to claim 4 wherein the alkaline solution is prepared by adjusting the pH of an aqueous solution of the polysaccharide to a value greater than 8, and the hydrogen peroxide and an aqueous solution of the ferric compound is added thereto.

8. A process according to claim 5 wherein the neutral solution is prepared by rendering neutral an aqueous solution of the polysaccharide, the hydrogen peroxide is added thereto, the solution is heated to boiling until the desired degree of degradation of the polysaccharide has resulted, the pH is adjusted to above 8, and the ferric compound is added.

9. A process according to claim 6 wherein the weak acid solution is prepared by rendering acidic an aqueous solution of the polysaccharide, hydrogen peroxide is added thereto, the solution is heated to boiling until the desired degree of degradation of the polysaccharide has resulted, the pH is adjusted to above 8, and the ferric salt is added.

10. A process according to any of claims 1—9 wherein the complex is recovered and dried, and redissolved in water to which a chelate forming hydroxy acid or salt has been added.

11. A process according to claim 10 wherein the chelate forming hydroxy acid or salt is added in an amount of from 2 to 10% by weight based on the weight of the polysaccharide iron complex.

12. A process according to claim 10 or 11 wherein the chelate forming hydroxy acid or salt is citric acid, tartaric acid, lactic acid, glycolic acid or salicyclic acid.

13. A process according to claim 1 substantially as hereinbefore described in any of Examples 1—5.

14. A process according to claim 1 substantially as hereinbefore described in any of Examples 6—8.

15. A colloidal iron preparation whenever prepared by a process according to any of claims 1—14.

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